1. A method of treating a patient having a cancer comprising administering to said patient a compound having the following formula:

10

men dent han the time

THE PLAN BUILD

15

1,71

wherein:

R₁ is H; C₁₋₂₄ alkyl; C₂₋₂₄ alkenyl; C₆₋₂₄ aryl; C₅₋₂₀ heteroaromatic ring; C₃₋₂₀ non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R₆; -C(O)OR₆; -C(O)NHR₆; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof, wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R₇;

[...t [...] 25

15

20

R₁ can also be a P(O)(OR')₂ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl; saleginyl, t-butyl, phosphate or diphosphate;

30

can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

35

 R_1

15

20

geng grass gents worst, pers result, th. H. 1286, th. H. 1886, th. H.

Harry Control

25

30

35

40

R₃ and R₄

is

 R_2

$$N$$
 N
 N
 R_3R_4N

case independently H; are in each alkyl; alkenyl; C_{2-24} C_{6-24} aryl; heteroaromatic ring; C3-20 non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and which and Gln, in each case optionally terminated by -R₇;

is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-1} 20 alkyl- C_{6-24} aryl, $C_{0,20}$ alkyl- C_{5-20} heteroaromatic ring, non-aromatic ring optionally containing heteroatoms selected from the group comprising O, N or S; and

is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} R_7 aryl, C₅₋₂₀ heteroaromatic ring, C₃₋₂₀ non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(0)R_6$, $-C(0)OR_6$, and

- X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4 ; or a pharmaceutically acceptable salt thereof.
- 2. A method according to claim 1, wherein at that least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$ or $-C(O)NHR_6$, then R_6 is other than H.
- 3. A method according to claim 1, wherein R_2 is of the formula:

$$0 \\ N \\ R_3 \\ R_4 \\ R_5$$

The first state of their man first days

int.

4. A method of treating a patient with cancer, wherein the cancer cells are deficient in nucleoside or nucleobase transporter proteins, comprising administering to said patient a compound according to the following formula:

30

35

wherein:

R₁ is H; $\mathring{\mathbb{C}}_{1-24}$ alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic

thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

10

 R_1 can also be a $P(O)(OR')_2$ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, or C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

15

 R_1 can also be monophosphate, diphosphate or triphosphate or mimetics thereof;

20

the thirty than much dien work it is along the little with the little water to the little with the little water to the little

)3 |s=6

sa h

 R_2 is

25

R₂R₄N N

X

30

each case independently H; R_3 and R_4 are in alkenyl; alkyl; C_{2-24} C_{6-24} aryl; C_{5-18} heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn

35

15

20

25

30

35

40

- and Gln, and which in each case is optionally terminated by $-R_7$;
 - R₆ is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl- C_{6-24} aryl, C_{0-20} alkyl- C_{5-18} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;
 - R_7 is, in each case, $C_{1\text{--}20}$ alkyl, $C_{2\text{--}20}$ alkenyl, $C_{6\text{--}10}$ aryl, $C_{5\text{--}10}$ heteroaromatic ring, $C_{3\text{--}20}$ non-aromatic ring optionally containing 1-3 heteroatoms selected

from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$, and

X and Y are each independently Br, Cl, I, F, OH, OR₃ or NR_3R_4 and at least one of X and Y is NR_3R_4 ; or a pharmaceutically acceptable salt thereof.

- 5. A method according to claim 4, wherein at least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(O)R_6$, $-C(O)OR_6$, or $-C(O)NHR_6$ then R_6 is other than H.
- 6. A method according to claim 4, wherein said cancer cells are deficient in one or more nucleoside or nucleobase transporter proteins that provide sodium-independent, bidirectional equilibrative transport.
 - 7. A method according to claim 4, wherein said cancer cells are deficient in nucleoside or nucleobase transporter proteins that provide sodium-dependent, inwardly directed concentrative processes.
 - 8. A method according to claim 7, wherein said cancer cells are deficient in nucleoside or nucleobase transporter proteins that provide sodium-dependent, inwardly directed concentrative processes.

- 5 9. A method according to claim 4, wherein said cancer cells are deficient in es transporter proteins, ei transporter proteins or both.
- 10 10. A method according to claim 4, wherein said cancer cells are deficient in cit transporter proteins, cib transporter proteins, cif transporter proteins, csg transporter proteins, cs transporter proteins, or combinations thereof.
 - 11. A method according to claim 4, wherein R_2 is of the formula:

12. A method of treating patients with cancer comprising administering to said patient a compound of the following formula:

wherein:

15

20

30

35

40

then much flutte fluit

12.0

R₁ is H; C₁₋₂₄ alkyl; C₂₋₂₄ alkenyl; C₆₋₂₄ aryl; C₅₋₂₀ heteroaromatic ring; C₃₋₂₀ non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R₆; -C(O)OR₆; -C(O)NHR₆; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gly, and which in each case is optionally terminated by -R₇;

R₁ can also be monophosphate, diphosphate, triophosphate or mimetics thereof;

15

 R_2 is

20

The transport of the tr

171

25

30

R₃ and R₄ are in each case independently H; C_{1-20} C_{2-20} alkenyl; C₆₋₁₀ aryl; C_{5-10} alkyl; heteroaromatic ring; C₃₋₂₀ non-aromatic ring containing optionally 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu,

15

20

25

30

Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and at least one amino acid is not Gly, and which in each case is optionally terminated by -R₇;

R₆ is, in each case, H, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₀.

alkyl- $C_{6\text{--}10}$ aryl, $C_{0\text{--}20}$ alkyl- $C_{5\text{--}10}$ heteroaromatic ring, $C_{3\text{--}20}$ non-aromatic ring optionally containing

1-3 heteroatoms selected from the group comprising O, N or S;

 R_7 is, in each case, $C_{1\text{--}20}$ alkyl, $C_{2\text{--}20}$ alkenyl, $C_{6\text{--}10}$ aryl, $C_{5\text{--}10}$ heteroaromatic ring, $C_{3\text{--}20}$ non-aromatic ring optionally containing 1-3 heteroatoms selected

from the group comprising O, N or S, $-C(0)R_6$, $-C(0)OR_6$, and

X and Y are each independently Br, Cl, I, F, OH, OR₃ or NR₃R₄ and at least one of X and Y is NR₃R₄; with the proviso that least one of R₁, R₃ and R₄ is other than H, and if R₃ and R₄ are both H and R₁ is $-C(0)R_6$, $-C(0)OR_6$, or $-C(0)NHR_6$ then R₆ is other than H; or

a pharmaceutically acceptable salt thereof; wherein said compound is administered at least daily for a period of 2 to 10 days.

13. A method according to claim 12, wherein R_2 is of the formula:

40 14. A method of treating a patient with cancer wherein the cancer is resistant to cytarabine, said method

comprising administering to said patient a compound according to the following formula:

10

is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-20} R_1 ring; C_{3-20} non-aromatic heteroaromatic optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(0)OR_6$; $-C(0)NRH_6$; or an amino acid radical or a dipeptide or tripeptide chain or mimetic thereof wherein the amino acids radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

15

20

Hall The Bridge County

226 1,30

laz b

25

30

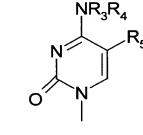
35

40

can also be a $P(0)(OR')_2$ group wherein R' is in R_1 each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

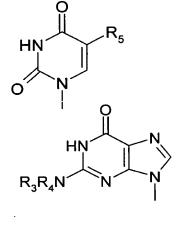
also be monophosphate, diphosphate, R_1 triphosphate or mimetics thereof;

is R_2



$$R_3R_4N$$

$$X \longrightarrow N \longrightarrow N$$



each case independently H; R_3 and R_4 are in alkenyl; C_{6-24} aryl; alkyl; C_{2-24}

25

30

35

The first first could be come to the state of the state o

ŧ

5 heteroaromatic ring; C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or a dipeptide or a tripeptide 10 chain or mimetic thereof wherein the amino acids are selected from the group comprising Glu, Gly, Ala, Val, Leu, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case 15 optionally terminated by $-R_7$;

> is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-1} R_6 $_{20}$ alkyl-C $_{6\text{-}24}$ aryl, C $_{0\text{-}20}$ alkyl-C $_{5\text{-}24}$ heteroaromatic C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

> R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{5-24} heteroaromatic ring, C_{3-20} non-aromatic 1-3 ring optionally containing selected from the group comprising O, N or S, $-C(0)R_{6}$, $-C(0)OR_{6}$; and

> X and Y are each independently Br, Cl, I, F, OH, OR3 or NR_3R_4 and at least one of X and Y is NR_3R_4 ; or a pharmaceutically acceptable salt thereof.

15. A method according to claim 14, wherein at least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(0)R_6$; $-C(0)OR_6$, or $-C(0)NHR_6$ then R_6 is other than H.

A method according to claim 14, wherein R_2 is of the formula:

II.

17. A method of treating a patient with cancer comprising:

determining that a compound enters cancer cells predominately by passive diffusion; and administering said compound to said patient; wherein said compound is a compound according to the formula:

$$R_1O$$
 R_2
 R_1O
 R_2
 R_2

15

10

wherein:

is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by $-R_7$;

2

a = #

g = h

25

20

30

R₁ can also be a P(O)(OR')₂ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-24} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

35

 R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

 R_2 is

$$\begin{array}{c|c}
 & NR_3R_4 \\
 & N \\
 & N
\end{array}$$

15

20

25

30

35

$$\begin{array}{c|c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

and R_4 are independently H; in each case alkyl; alkenyl; C1-24 C_{6-24} heteroaromatic ring; C_{3-24} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn Gln, and which in each case optionally terminated by -R7;

R₆ is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl- C_{6-24} aryl, C_{0-20} alkyl- C_{5-24} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

R₇ is, in each case, $C_{1\text{-}24}$ alkyl, $C_{2\text{-}24}$ alkenyl, $C_{6\text{-}24}$ aryl, $C_{5\text{-}24}$ heteroaromatic ring, $C_{3\text{-}20}$ nonaromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(0)R_6$, $-C(0)OR_6$, and

X and Y are each independently Br, Cl, I, F, OH, OR₃ or NR_3R_4 and at least one of X and Y is NR_3R_4 ; or a pharmaceutically acceptable salt thereof.

18. A method according to claim 17, wherein at least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(0)R_6$ or $-C(0)OR_6$, then R_6 is other than H.

20. A method of treating a patient with cancer comprising:

administering to said patient a compound which has been determined to enter the cancer cells predominately by passive diffusion, wherein said compound is a compound according to the formula:

20

,[]

and b

$$R_1O$$
 R_2
 O
 R_2
 O
 O

wherein:

 R_1

30

25

is H; C₁₋₂₄ alkyl; C₂₋₂₄ alkenyl; C₆₋₂₄ aryl; C₅₋₂₄ heteroaromatic ring; C₃₋₂₄ non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R₆; -C(O)OR₆; -C(O)NHR₆; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R₇;

35

 R_1 can also be a P(O)(OR')₂ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-18} arylmethyl, C_{2-18} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

 R_1 also monophosphate, diphosphate, can be triphosphate or mimetics thereof;

is R_2

10

$$NR_3R_4$$
 NR_3R_4
 NR_5
 NR_5

20

15

a the start that acut thus, most that, if į ---25

je b 7

30

35

40

each case independently and R4 are in C_{1-24} alkenyl; alkyl; C_{2-24} C_{6-24} aryl; C_{5-24} heteroaromatic ring; C₃₋₂₀ non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn Gln, and which in each optionally terminated by $-R_7$;

is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-1} R_6 ₂₀ alkyl- C_{6-24} aryl, C_{0-20} alkyl- C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} R_7 aryl, C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms

selected from the group comprising O, N or S, $-C(0)R_{6}$, $-C(0)OR_{6}$; and

X and Y are each independently Br, Cl, I, F, OH, OR3 or NR_3R_4 and at least one of X and Y is NR_3R_4 ; or a pharmaceutically acceptable salt thereof.

10

21. A method according to claim 20, wherein at least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(0)R_6$; $-C(0)OR_6$ or $-C(0)NHR_6$ then R_6 is other than H.

15

A method according to claim 20, wherein R_2 is of the formula:

25

$$O = N R_3 R_4 R_5$$

30

A method of treating a patient with cancer resistant to troxacitabine, comprising administering to said patient a troxacitabine derivative having a greater lipophilicity than troxacitabine.

35 24. method according to claim 23, wherein Α said derivative is a compound of the following formula:

40

wherein:

45

 R_1 is H; C_{1-24} alkyl; C_{2-24} alkenyl; C_{6-24} aryl; C_{5-24} heteroaromatic ring; C_{3-20} non-aromatic optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; $-C(O)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or

25

30

35

113

طعودا

*** .,,,

- dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln and the amino acid chain contains at least one amino acid other than Gly, and which in each case is optionally terminated by $-R_7$;
- R_1 can also be a P(O)(OR')2 group wherein R' is in 15 each case independently H, C₁₋₂₄ alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-24} arylmethyl, acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;
 - R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;
 - is R_2

R₃ and R₄ are in each case independently H; 40 alkyl; C_{2-20} alkenyl; C₆₋₁₀ aryl; C₅₋₁₀ heteroaromatic ring; C3-20 non-aromatic ring optionally containing 1-3 heteroatoms

25

30

40

comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln and the amino acid chain contains at least one amino acid other than Gly, and which in each case is optionally terminated is, in each case, H, C₁₋₂₀ alkyl, C₂₋₂₀ alkenyl, C₀₋ 20 alkyl- C_{6-10} aryl, C_{0-20} alkyl- C_{5-10} heteroaromatic

non-aromatic C_{3-20} ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S; is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} R_7

aryl, C₅₋₁₀ heteroaromatic ring, C₃₋₂₀ non-aromatic 1-3 optionally containing heteroatoms selected from the group comprising O, N or S, $-C(O)R_6$, $-C(O)OR_6$, and

X and Y are each independently Br, Cl, I, F, OH, OR3 or NR₃R₄ and at least one of X and Y is NR₃R₄; with the proviso that least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(0)R_6$, $-C(0)OR_6$ or $-C(0)NHR_6$, then R_6 is other than H; or a pharmaceutically acceptable salt thereof.

A method according to claim 24, wherein R_2 is of the 35 25. formula:

per, and the tree is a test. 13 ļ.zk .75



A. Conti

26. A method of treating a patient with cancer comprising:

determining that a compound does not enter cancer cells predominately by nucleoside or nucleobase transporter proteins; and administering said compound to said patient; wherein said compound is a compound according to the formula:

15

20

25

wherein:

R₁ is H; C₁₋₂₄ alkyl; C₂₋₂₄ alkenyl; C₆₋₂₄ aryl; C₅₋₂₀ heteroaromatic ring; C₃₋₂₀ non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; -C(O)R₆; -C(O)OR₆; -C(O)NHR₆; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which in each case is optionally terminated by -R₇;

30

R₁ can also be a P(O)(OR')₂ group wherein R' is in each case independently H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{7-24} arylmethyl, C_{2-17} acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} S-acyl-2-thioethyl, saleginyl, t-butyl, phosphate or diphosphate;

35

 R_1 can also be monophosphate, diphosphate, triphosphate or mimetics thereof;

R₂ is

10

15

20

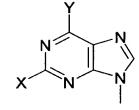
25

30

35

40

R₃R₄N N N



each case independently H; R₃ and R₄ are in C_{2-24} alkenyl; alkyl; C_{6-24} aryl; C5-24 heteroaromatic ring; C3-20 non-aromatic ring containing 1-3 optionally heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NHR_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn Gln, and which in each case optionally terminated by -R7;

R₆ is, in each case, H, C_{1-24} alkyl, C_{2-24} alkenyl, C_{0-20} alkyl- C_{6-24} aryl, C_{0-20} alkyl- C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S;

 R_7 is, in each case, C_{1-24} alkyl, C_{2-24} alkenyl, C_{6-24} aryl, C_{5-20} heteroaromatic ring, C_{3-20} non-aromatic

10

15

ring optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(0)R_6$, $-C(0)OR_6$; and

X and Y are each independently Br, Cl, I, F, OH, OR_3 or NR_3R_4 and at least one of X and Y is NR_3R_4 ; or a pharmaceutically acceptable salt thereof.

27. A method according to claim 26, wherein at least one of R_1 , R_3 and R_4 is other than H, and if R_3 and R_4 are both H and R_1 is $-C(0)R_6$, $-C(0)OR_6$ or $-C(0)NHR_6$ then R_6 is other than H.

28. A method according to claim 27, wherein R_2 is of the formula:

$$O = N + NR_3R_4$$

$$O = N + R_5$$

25

Hardy Walter and Year agent to be their

12

|====

|sek

30 129.

A method according to any one of claims 1-28, wherein said cancer is prostate cancer, colon cancer, lung cancer, melanoma, ovarian cancer, renal cancer, breast cancer, lymphoma, pancreatic cancer or bladder cancer.

- 30. A method according to any one of claims 3-28, wherein said cancer is leukemia.
- 31. A method according to any one of claims 1-28, wherein at least one of R_1 , R_3 , or R_4 is piperazinyl, piperidinyl, morpholinyl, pyrrolidinyl, adamantyl or quinuclidinyl.
- 32. A method according to any one of claims 1-28, wherein at least one of R_1 , R_3 or R_4 is acetyl, propionyl, butyryl, valeryl, caprioic, caprylic, capric, lauric, myristic, palmitic, stearic, oleic, linoleic, or linolenic.

- 5 33. A method according to any one of claims 1-28, wherein at least one of R₁, R₃ or R₄ is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, napthyl or biphenyl.
- 34. A method according to any one of claims 1-28, wherein at least one of R_1 , R_3 or R_4 contains a heterocyclic group selected from the following group:

furyl, thiophenyl, pyrrolyl, imidazolyl, pyrazoyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl triazolyl, tetrazolyl, oxadrazolyl,

thiadiazolyl 15 thiopyranyl, pyrazinyl, benzofuryl, benzothiophenkl, indolyl, benzimidazolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiozolyl, benzisothiazolyl benzoxadiazolyl, quinolinyl, carbazolyl, acridinyl, cinnolinyl isoquinolinyļ, 20 quinazolinyl!

35. A method according to any one of claims 1-28, wherein said compound is administered at least daily for a period of 2 to 10 days every 2 to 5 weeks.

- 36. A method according to any one of claims 1-28, wherein said compound is administered at least daily for a period of 2 to 10 days every 3 to 4 weeks.
- 30 37. A method according to any one of claims 1-28, wherein said compound is administered at least daily for 3 to 7 days every 2 to 5 weeks.
- 38. A method according to any one of claims 1-28, wherein said compound is administered at least daily 4 to 6 days every 2 to 5 weeks.
 - 39. A compound having the following formula:

224

25

21

electer

| | 5 | wherein: \ |
|---|-----|--|
| | | R_1 \(\sqrt{is}\) H; C_{1-20} alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} |
| | | heteroaromatic ring; C_{3-20} non-aromatic ring |
| | | optionally containing 1-3 heteroatoms selected |
| | | from the group comprising O, N, or S; $-C(0)R_6$; |
| | 10 | $-C(O)OR_6$; $-C(O)NRH_6$; or an amino acid radical or |
| | | dipeptide or tripeptide chain wherein the amino |
| | | acid radicals are selected from the group |
| | | comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, |
| | | Phe Tyr, Trp, Ser, Thr, Met, Cys, Asn and Gln, |
| | 15 | and which in each case is optionally terminated |
| | | by $-\mathbb{R}_7$; |
| | | |
| [2] | | R_1 can also be a P(O)(OR') ₂ group wherein R' is in |
| Auch groß einig den ning if, it, dent Math fhadt of then some thata that it is a single that the single | | each case independently H, C_{1-20} alkyl, C_{2-20} |
| 1 | 20 | alkenyl, C_{6-10} aryl, C_{7-11} arylmethyl, C_{2-7} |
| | | acyloxymethyl, C_{3-8} alkoxycarbonyloxymethyl, C_{3-8} |
| ; * F | | S-acyl-2-thioethyl, saleginyl, t-butyl, |
| 1, | | phosphate or diphosphate; |
| a=b | 0.5 | |
| 107 | 25 | R_1 can also be monophosphate, diphosphate, |
| 1,37 | | triphosphate or mimetics thereof; |
| | | |
| ican | | R_2 is |
| | 30 | NR ₃ R ₄ |
| | | |
| | | N HN 1.5 |
| | | |
| | | O'N' |
| | 35 | ¹ \ |
| | | CI Y |
| | | $N \longrightarrow N$ |
| | | R_3R_4N |
| | | R_3R_4N |
| | 40 | R_3 and R_4 are in each case independently H; C_{1-20} |
| | | alkyl; C_{2-20} alkenyl; C_{6-10} aryl; C_{5-10} |
| | | heteroaromatic ring; C_{3-20} non-aromatic ring |
| | | ; : : : : : : : : : : : : : : : : : : : |

containing 1-3 5 optionally heteroatoms selected from the group comprising O, N, or S; $-C(0)R_6$; $-C(0)OR_6$; $-C(0)NRH_6$; or an amino acid radical or dipeptide or tripeptide chain or mimetic thereof wherein the amino acid radicals are selected from the group 10 comprising Glu, Gly, Ala, Val, Leu, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn Gln, and which in each and case optionally terminated by -R7; is, in each case, H, C_{1-20} alkyl, C_{2-20} alkenyl, C_{0-1} 15 R_6 $alkyl-C_{6-10}$ aryl, C_{0-20} alkyl- C_{5-10} heteroaromatic non-aromatic ring optionally C₃₋₂₀ containing 1-3 heteroatoms selected from the group comprising O, N or S; is, in each case, C_{1-20} alkyl, C_{2-20} alkenyl, C_{6-10} 20 R_7 aryl, \setminus C₅₋₁₀ heteroaromatic ring, C₃₋₂₀ nonaromatic optionally containing 1-3 heteroatoms selected from the group comprising O, N or S, $-C(0)R_6$ $-C(0)OR_6$; and X and Y are each independently Br, Cl, I, F, OH, OR₃ 25 or NR₃R₄ and at least one of X and Y is NR₃R₄; or a pharmaceutically acceptable salt thereof; with the \proviso that at least one of R_1 , R_3 and R₄ is 30 C₇₋₂₀ alkyl C7-20 alkenyl; C₆₋₁₀ aryl; C₅₋₁₀ heteroaromatic ring; C_{4-20} non-aromatic ring optionally containing 1-3 heteroatoms selected from the group comprising O, N, or S; 35 $C(0)R_6$ in which R_6 is 1, C_{7-20} alkyl, C_{7-20} alkenyl, C_{0-20} alkyl- C_{6-10} aryl, C_{0-20} alkyl- C_{5-10} heteroaromatic ring, ring optionally containing non-aromatic heteroatoms selected from the group comprising O, N or S; $-C(0)OR_6$ in which R_6 is C_{7-20} alkyl, C_{7-20} alkenyl, 40 C_{0-20} alkyl- C_{6-10} aryl, C_{0-20} alkyl- C_{5-10} heteroaromatic ring,

١

optionally containing

ring\

non-aromatic

 C_{4-20}

5 heteroatoms selected from the group comprising O, N or S; or

a dipeptide or tripeptide or mimetic thereof where the amino acid radicals are selected from the group comprising Glu, Gly, Ala, Val, Leu, Ile, Pro, Phe, Tyr, Trp, Ser, Thr, Cys, Met, Asn and Gln, and which is optionally terminated by $-R_7$.

40. A method of treating a patient with cancer comprising administering to said patient a prodrug form of troxacitabine, having a lipophilic structure to enhance entry of the prodrug into the cancer cells by passive diffusion, wherein said lipophilic structure is cleavable by cellular enzymes, thereby increasing the amount of troxacitabine within the cancer cells to a level greater than that allowable by administration of troxacitabine in nonprodrug form

41. A method of treating a patient having cancer which is resistant to generate to comprising administering to said patient a troxacitable derivative having a lipophilic structure which enhances the entry of the derivative into the cancer cell by the passive diffusion.

42. A method of treating a patient having cancer wherein the cancer cells are deficient in nucleoside or nucleobase transporter proteins, comprising administering to said patient a troxacitabine derivative having a lipophilic structure which enhances entry of the derivative into the cancer cells by passive diffusion.

43. A method according to claim 4, wherein said cancer cells are deficient in one or more nucleobase transporter proteins.

44. A method according to any one of claims 1-28, wherein the compound is of the formulas

20 5

1,77

 10

15

25

30

35

n D

Post

NO₂

gash greet, glath, seeng gase receip is it gleeth it it should be the second black though the state of the second black though the state of the second black that it is a : 5 | | | |

a e la 7

[2]

es k

10

A method according to any one of claims 1 to 28 45. wherein the compound is of the formula

ŔO

15

A method according to any one of claims 1 to 28, wherein the compound is of the formula

245 A method according to any one of claims 1 to 28, wherein the compound is selected from 4-HEXYL-BENZOIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL) $-\sqrt{1}$ 3] DI ϕ XOLAN-2-YLMETHYL ESTER (No. 191); 8-PHENYL-OCTANOIC ACID [1-(2-HYDROXYMETHYL-[1,3] h 10x Ox An-4-YL -2-0x 0-1 -2-DIHYDRO-PYRIMIDIN-4-YL]-AMTDE (No. 197); -PHENYL-OCTANQIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN-1-YL) - [1, 3] DIOXQLAN-2-YLMETHYL ESTER (No. 198); $4-PENTYL \rightarrow BIGYCLO[2, 2.2]OCTANE-1-CARBOXYLIC ACID 4-(4-$ 15 YLMETHYL ESTER (No. 211); 4-PENTYL-CYCLOHEXANECARBOXYLIC ACID 4-(4-AMINO-2-OXO-2H-PYRIMIDIN+1-YL)-[1,3]DIQXOLAN-2-YLMETHYL ESTER (No. 240) or mixtures thereof. 20